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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/517,016	08/18/95	MARSHALL W	31017-011

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EXAMINER	
ZEMAN, M	
ART UNIT	**PAPER NUMBER**
1815	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/30/96.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

* U.S. GPO: 1996-410-238/40050

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1815.

2. Applicant's election of Group I, claims 1-14 in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

3. Claim 8 is objected to because of the following informalities: the term "non-pathogen." should not be abbreviated with a period following. A claim should be one sentence, ending with one period. Appropriate correction is required.

4. Claim 6 is objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim must refer to other claims in the alternative only. See MPEP § 608.01(n). See paragraph 7 of this action for details as to the further treatment of this claim.

Claim Rejections - 35 USC § 112

5. Claims 4, 5, 7, 8, 10, 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "said non-nutritive isotonic solution" in reference to claim 2. There is insufficient antecedent basis for this limitation in the claim. Neither claim 2 nor claim 1 use this terminology.

The metes and bounds of the term "an effective amount" in claim 5 are unclear. There is no disclosure as to how much of any of the claimed factors is required in order to modulate macrophages in an animal. No minimum or maximum dosages are given, nor is a range of effective amounts disclosed.

The metes and bounds of the phrase "to modulate macrophages" in claim 5 are unclear. The parameters of macrophages that are being modulated are not disclosed. A macrophage can be activated through many pathways, as it can also be repressed through many pathways. It can be induced to produce cytokines and other factors, and it can be induced to phagocytize a pathogen. None of these specific effects are recited in the claims, nor is it clear from the specification as to what applicant intends to encompass in this phrase.

Claim 7 recites the limitation "said selected bacteria" in reference to claim 6. There is insufficient antecedent basis for this limitation in the claim. Neither claim 6 nor claim 5 use this terminology.

Claim 8 recites the limitation "said commensal bacteria" in reference to claim 6. There is insufficient antecedent basis for this limitation in the claim. Neither claim 6 nor claim 5 use this terminology.

Claim 10 recites the limitation "said bacteria" in reference to claim 5. There is insufficient antecedent basis for this limitation in the claim. Claim 5 does not use this terminology.

Claims 11 and 12 are drawn to SRFs comprising "a molecular weight of less than about 50 (or 10) kDa." It is unclear as to whether all of the components of the composition should add up to the specified molecular weight, or whether one singular SRF would have the specified molecular weight.

6. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 14 is drawn to synthesis or cloning of the claimed SRF's. There is no basis in the specification as filed for the chemical synthesis or cloning and recombinant expression of these factors. No amino acid or DNA sequences are disclosed, nor are any specific proteins, or polypeptides responsible for the immunomodulatory effect disclosed.

Claim Clarification

7. Due to the several instances of rejections due to lack of antecedent basis and improper dependent claims, the examiner has tried to reconstruct the claims in light of the invention for the purposes of the application of prior art as follows:

Claim 4 will be examined as if claim 2 recited "wherein step (b) comprises placing the bacteria in a non-nutritive isotonic solution."

Claim 6 will be examined as a composition of SRF's resulting from the method of claim 1.

Claims 7, 8, and 9 will be examined as dependent from claim 6 which is being examined as dependent from claim 1.

Claim 10 appears to be a further method step of claim 1. The claims recites a selection step for the identification of bacteria which exert an effect upon an immune response. Claim 10 will be examined as if it depended from claim 1, as a further step in the claimed method.

These changes were attempted in the interests of compact prosecution, however, this does not alleviate the burden upon the applicant to respond to the rejections under 35 U.S.C. 112, second paragraph, or the objection made under 37 C.F.R. 1.75(c).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-9 are product-by-process type claims. The MPEP discusses product-by -process claims in chapter 2100: "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by -process claim is the same as, or obvious from a product in the prior art, the claim is unpatentable even though the prior product was made by a different process." See MPEP 2113.

9. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by De Vuyst.

Claims 1-4 and 10 are drawn to a method of making stress response factors by subjecting the bacterial culture to a stress such as non-nutritive or low nutritive media, altered pH, and increased biomass, and analyzing their effect on an immune response. Claims 5-9 are drawn to compositions comprising the factors, wherein the bacteria stressed is a Lactobacillus. Claim 11 specifies that the factor be about 50 Kd or less, and claim 12 specifies the factor is about 10 Kd or less. Claim 13 describes the composition as being measured at OD_{255}. De Vuyst (De Vuyst et al 1996 April v 142 (4) p 817-827) discloses the production of bacteriocin, an anti-microbial compound, from Lactobacillus amylovorus under several stressed conditions including low temperatures, non-nutritive or toxic media, change in pH, and an increase in biomass. The bacteriocin complex is approximately 30 Kd, while the monomer appears to be about 6 Kd.

Concentrations of bacteriocin were calculated using OD readings at OD_{260}. These bacteriocin compositions could be used to enhance the response to bacterial infection.

10. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Hata.

Claims 1-4 are drawn to a method of making factors capable of modulating the immune response of a patient by subjecting the bacterial culture to a non-nutritive or low nutritive media. Hata (US Patent 4,314,995) discloses a Lactobacillus strain that is able to grow in a low or non-nutritive media, (containing sodium chloride).

11. Claims 1, 5, 6 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by van den Broek.

Claims 1 and 10 are drawn to methods of making stress response factors, by the stressing of bacteria, collecting the factor, and measuring its immunomodulatory effects on an immune response. Claims 5 and 6 are drawn to the compositions comprising the factors. van den Broek (van den Broek et al. 1989 J Exp Med 170 449-466) discloses a method of making a heat shock protein by heat stressing mycobacteria and collecting the protein that results. This heat shock protein was found to modulate the immune response of a rat to the induction of arthritis.

12. Claims 5, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lydyard.

Claims 5, 11, and 12 are drawn to compositions of stress response factors that are less that 50 Kd or less than about 10 Kd. Lydyard reviews the several classes of heat shock proteins,

produced by bacteria under heat stress, including the class of lower molecular weight stress proteins having molecular weights of 10-30 Kd.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Vuyst in view of Kuwabara, and Kato.

De Vuyst discloses factors produced by a Lactobacillus that are released from the Lactobacillus under stressful conditions such as increased biomass, change in pH, low temperature, and levels of toxins in the media. These factors could enhance an immune

response. Kuwabara (Kuwabara et al 1988 Jpn J Vet Sci 50 (3) p 665-72) and Kato (Kato et al 1983 Microbiol Immunol. 27 (7) 611-618) both disclose that the administration of Lactobacillus results in the activation of macrophages. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have stressed Lactobacillus in any of the manners as disclosed by De Vuyst which would have induced the production or release of factors able to modulate an immune system response. One would have expected factors that affect the immune response to have been made by this procedure, as preparations of the Lactobacillus itself had been shown by Kuwabara and Kato to be capable of activating macrophages.

Conclusion

15. No claim is allowed.

16. The following articles cited but not relied upon are considered pertinent to Applicant's disclosure.

Becker and Brendel 1996 Current Microbiology Vol 32 (4) p 232-236. Becker discloses two Lactobacillus genes that encode heat shock proteins.

Popova et al. 1993 Int. J. Immunopharmac. Vol 15 (1) p 25-37 . Popova discloses the stimulatory effect of a Lactobacillus oral preparation on monocytes and macrophages.

Perdigon et al. 1990 J Food Protection Vol 53 (5) 404-410. Perdigon discloses the increase in mucosal intestinal immunity upon administration of an oral administration of Lactobacillus.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 8:00 am and 5:30 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800

mkz
March 12, 1997